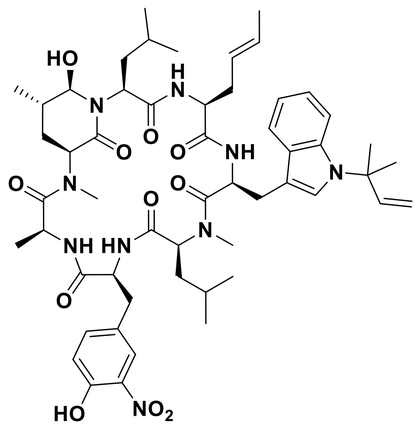
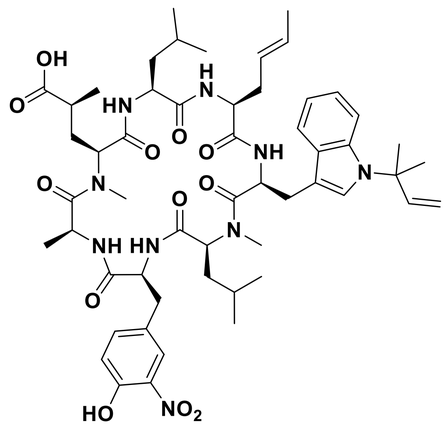
Total Synthesis of Rufomycin Derivatives[1]

Jennifer Greve, Uli Kazmaier
Department of Organic Chemistry, Campus C4.2, Saarland University, 66123 Saarbrücken, Germany
s9jegrev@stud.uni-saarland.de

UNIVERSITÄT DES SAARLANDES



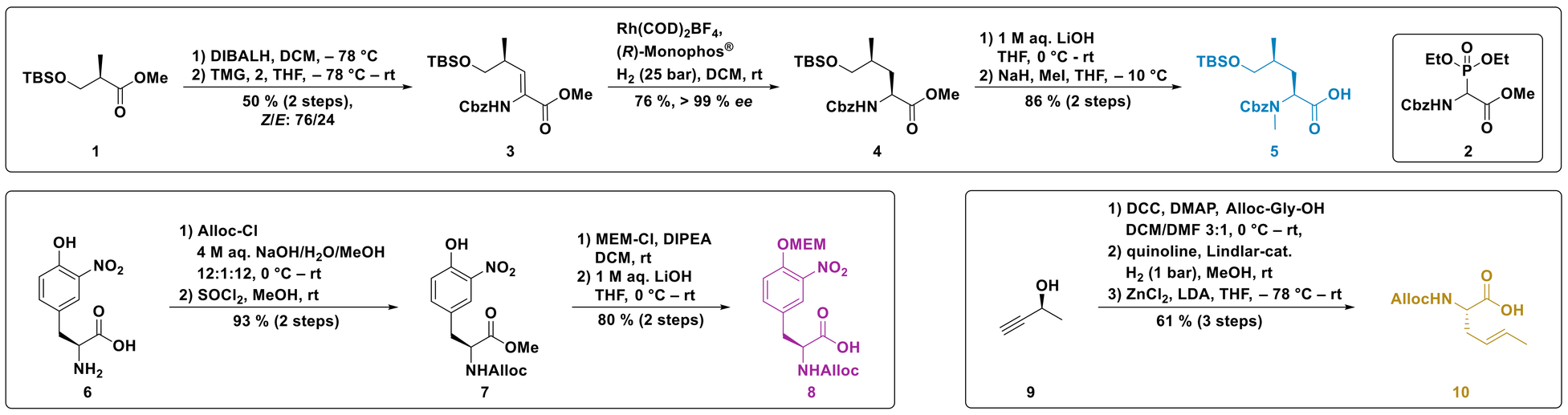
Rufomycin 21



Rufomycin 23

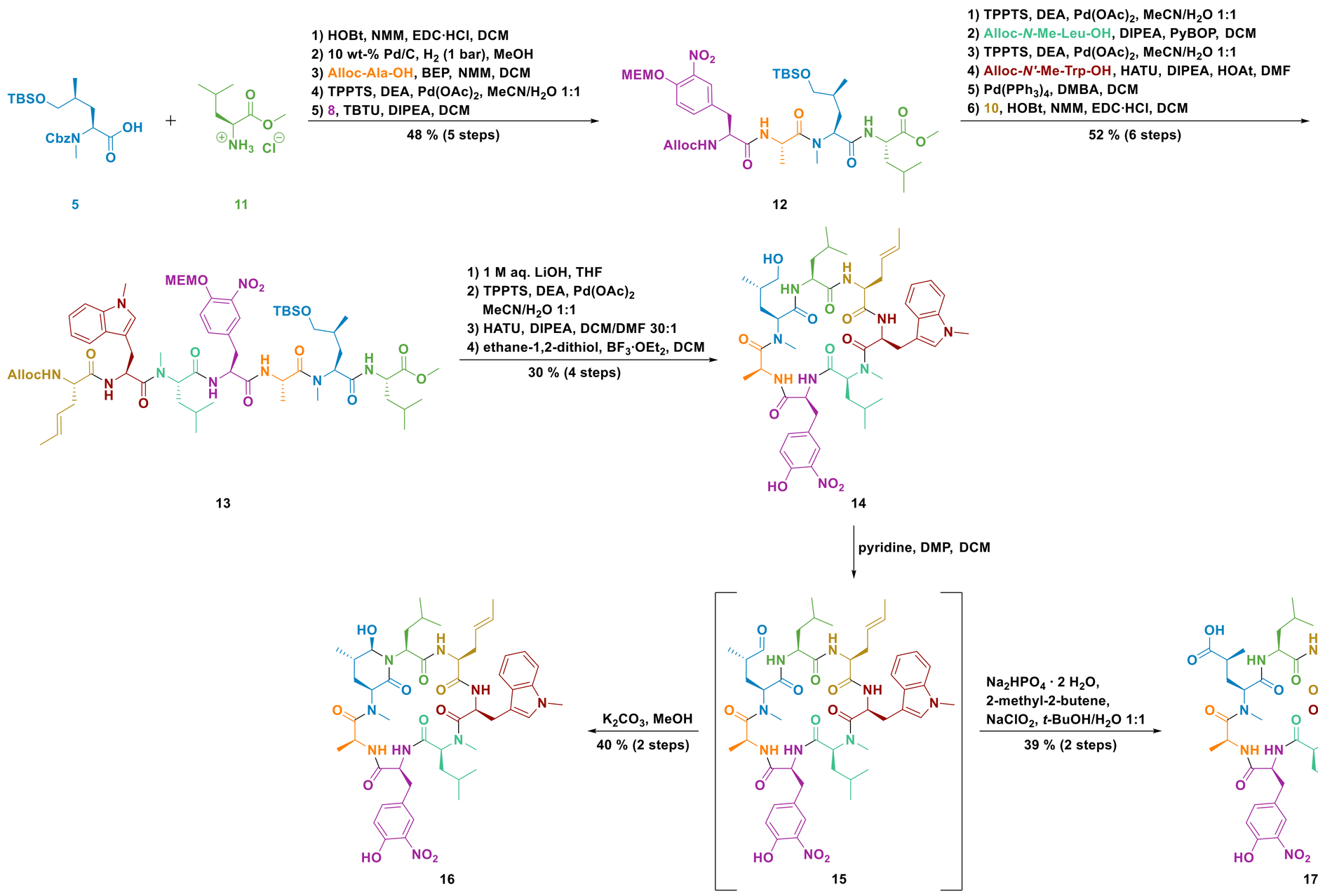
Rufomycins are cyclic heptapeptides which exhibit potent biological activity against multidrug-resistant isolates of *Mycobacterium tuberculosis.* They contain four non-proteinogenic amino acids: 2-amino-4-hexenoic acid (AHA) is unique and has not been observed in any other natural product, 3-nitro-tyrosine is a structural motif rarely found in peptides.[2] γ-hydroxyleucine as well as the tryptophan unit are also found in the structurally related Cyclomarins.[3] In the 1960s, the first Rufomycins were isolated from *Streptomyces atratus* nov. sp. or *Streptomyces islandicus.*[4,5] To date, several more Rufomycins have been discovered.[6]

Synthesis of the non-proteinogenic Amino Acids



Synthesis of the Rufomycin Derivatives

For the assembly of the heptapeptides, a linear linkage strategy from the C- to the N-terminus starting from leucine was chosen. Consequently, the macrolactamisation was carried out between the Leu and the AHA unit. Subsequent oxidations to derivatives **16** and **17** were performed according to the experimental procedure of Guo and Ye, who published the total synthesis of Rufomycins 21 and 23 in 2018.[7]



Two Rufomycin derivatives, **16** and **17**, bearing an *N*'-methylated Trp unit were synthesised. Derivative **16** is structurally related to Rufomycin 21 while derivative **17** is similar to Rufomycin 23. The prenyl residue in the Trp side chain was omitted because in the case of the Cyclomarins, an exchange to *N'*-methyl-tryptophan was possible without a significant loss of biological activity.[8]

MIC	16	17
***M. tuberculosis* H37Ra**	**0.05 µM**	**16.2 µM**

[1] J. Greve, A. Mogk, U. Kazmaier*, *Mar. Drugs* **2022**, *20*, 632.
[2] J. Ma et al., *Nat. Commun.* **2017**, *8*, 1–10.
[3] W. Fenical, J. Clardy et al., *J. Am. Chem. Soc.* **1999**, *121*, 11273–11276.
[4] K. Nakazawa et al., *Rufomycin. US 3,655,879* **1961**.
[5] T. Takita et al., *J. Antibiot. Ser. A* **1962**, *15*, 46–48.
[6] J. B. McAlpine et al., *J. Nat. Prod.* **2021**, *84*, 2644–2663.
[7] Y. Guo, T. Ye et al., *Org. Lett.* **2018**, *20*, 6166–6169.
[8] U. Kazmaier et al., *Chem. Eur. J.* **2019**, *25*, 8894–8902.